Modern Concepts of Cardiovascular Disease

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DRUGS USED IN THE TREATMENT OF CARDIOVASCULAR DISEASES: II. CAFFEINE, CAMPHOR, AND STRYCHNINE GROUPS

These groups of drugs are discussed together because they all affect mainly the vasomotor system, and they all exert a pharmacologic action on nervous centers. Their chief therapeutic use is in conditions associated with failure of the peripheral vascular system, particularly in acute collapse such as occurs in infectious diseases and following traumata to the central nervous system. It is suggestive that the therapeutic possibilities of some of these substances are greater than is at present appreciated. The problem will be answered definitely only when the clinical interrelation between the central nervous system and vascular tone is better understood.

A. *The Caffeine Group.* The details of the pharmacologic action of this group in the intact animal and in man are not sufficiently understood; hence the therapeutic rationale is not firmly established. In man, just as in animals, when administered in large therapeutic doses caffeine may act directly on the heart, but its most important effects are exerted upon the vessels. The effect on the heart depends partly on a central vagus action, partly on changes induced in the intracardiac conduction system, and partly on a dilator action on the coronary vessels. There may also be an effect on the cardiac muscle itself. The changes in the vascular system depend mainly on the action of caffeine on the medullary vasomotor centers, but there is probably a direct action on the vascular wall as well. The coronary, cerebral, splanchnic and renal vessels are particularly apt to show changes. In large doses caffeine may induce stimulation of the respiration, and also of cortical functions. Comatose patients may temporarily become conscious.

On the whole, caffeine is an emergency drug. It is indicated in acute circulatory collapse during and after surgical operation and in infectious diseases, particularly in pneumonia. Clinically its beneficial effect manifests itself in a prompt change from a state of stupor with low arterial pressure, rapid heart rate, collapsible pulse and cyanosis, to a rational state with normal blood pressure, increased fullness of the pulse, and disappearance of cyanosis. Caffeine is not, as a rule, used as a diuretic for cardiac dropsies. Its continued use with digitalis in failure of the heart due to organic heart disease is not rational.

Caffeine is practically insoluble in water; hence it is administered in the form of its sodium benzoate and sodium salicylate salts. The single dose is usually from 0.5 to 1.0 Gm. (gr. 7 to 15). It is absorbed from the gastrointestinal canal, but as it is used mainly in emergencies it should be given intramuscularly or intravenously. When given subcutaneously it induces pain and irritation, and is absorbed relatively slowly. If the circulation is poor, local necrosis of the tissues may develop even when the caffeine is administered intramuscularly. We have observed such sterile local muscular abscesses in a number of patients with pneumonia. In patients with bacteriemia the organism may eventually become localized in the site of injection.

The duration of the effect of caffeine, unless further spontaneous improvement follows, is from two to three hours. This period corresponds to the persistence of action of the drug; hence the dose may be repeated at the end of such intervals. In milder intoxication the manifestations consist in palpitation, premature beats, insomnia, nausea, vomiting, vertigo and headaches. Severe caffeine poisoning in man is comparatively rare. We have had an opportunity to observe one case, however, in which delirium and convulsions were present.

The other members of this group are quite closely related to caffeine both in their chemical composition and in their pharmacologic action. Theobromine (dimethylxanthine) exerts relatively less effect on the central nervous system, but is more effective as a coronary dilator. It is claimed, also, that it is a more effective diuretic than caffeine. This is questionable, however, as the difference can be explained by the larger doses used. Theobromine sodium salicylate is given in doses of 0.75 to 1.5 Gm. (gr. 12 to 22) three or four times daily in cases of angina pectoris, coronary sclerosis, and cardiac pain due to aortitis and arterial hypertension. If used as a diuretic it should be given for two to three days. Some sensitive patients may develop nausea, vomiting or diarrhea.

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Theophylline or theocin (1.3 dimethyl—2.6 dioxypurine) is a distinctly better diuretic than either caffeine or theobromine. It is also an effective dilator of the coronary vessels. It is given in doses of 0.1 to 0.3 Gm. (gr. 1½ to 4) three times daily. Theophylline - ethylenediamine (euphyllin), in doses of 0.1 Gm. (gr. 1½) three to four times daily, is also used as an effective dilator of the coronary vessels, and as a diuretic. The side action on the nervous centers is less pronounced than in the case of caffeine.

B. *The Camphor Group.* The exact therapeutic evaluation of this group of drugs is even more difficult than with the caffeine group. On the whole, the American School is rather skeptical of its value in circulatory disorders. Cushny, for example, has stated that "in man and animals the heart is sometimes slowed, but is generally little affected in either strength or rate"; and that "the slight dilatation of the vessels (of the skin) is the only change in the circulation, unless quantities sufficient to cause convulsions are injected." Some of the outstanding representatives of the Continental School, for example, Gottlieb and Meyer, however, have emphasized that "in the conditions of the circulatory failure, where stimulus production in the heart threatens to fail, camphor is undoubtedly to be considered a heart stimulant." From a limited experimental pharmacologic and therapeutic experience, I am somewhat inclined to agree with the latter statement, particularly in so far as the more recently introduced synthetic preparations are concerned.

There are a number of experimental studies available indicating that while camphor exerts no appreciable effect on the normal heart, under induced myocardial weakness it can strengthen the heart action. The changes in the blood pressure and the peripheral vessels that are observed in animals after the intravenous application of camphor preparations are caused by the action on vasomotor centers, rather than by a direct action on the vessels. In man, also, a beneficial effect is observed in conditions that depend mainly on depressed nervous centers. Thus, in cases of collapse caused by non-organic cardiac condition, or by vasomotor failure such as occurs in postoperative and traumatic collapse, or in shock due to hemorrhage, strikingly rapid improvement is at times observed.

The use of camphor has been discredited for several reasons: It is relatively slowly absorbed from the intestinal canal, and once it enters the blood, promptly changes into camphor glucuronic acid. Moreover, it is ineffective even when administered hypodermically in sterile olive oil in doses of from 0.06 to 0.18 Gm. (gr. 1 to 3), or when administered intravenously as camphor water. The concentration in the blood serum following such administration is insufficient. If, however, from 2 to 6 c.c. of a 20 per cent solution in olive oil is injected intravenously, one can observe improvement in cases of collapse. The cyanotic color of the face becomes normal, and the thready pulse fuller.

Because of the difficulty of administering camphor in high concentrations without oily solution, other more soluble preparations have been introduced in recent years. Among these is Methyl isopropyl cyclohexenon ("hexeton"). Its sodium salicylate is prepared in 1 per cent and 10 per cent solutions. It is claimed that in animals this preparation is more effective than camphor in elevating the blood pressure and in stimulating respiration. Clinically, because of its greater concentration and per[illegible]s because of its slower detoxication, it may produce a relatively greater stimulation of the vasomotor tone of the respiration after intravenous administration than does camphor. After subcutaneous and intramuscular administration I have observed no appreciable change. The effect of intravenous administration is transient, and is perhaps not entirely without danger. If circulatory and respiratory collapse exist simultaneously, it may also help to induce better respiration.

Other preparations of the group are Pentamethylenetetrazol ("cardiazol"), which is used intramuscularly in doses of 1 c.c. (15 minims) of a 10 per cent solution; and pyridine carbonate of diethylamide ("coramine"), used in doses of 1 c.c. of a 26 per cent solution either intramuscularly or by slow intravenous injection. Both of these preparations may be administered orally, but their effectiveness is questionable.

C. *The Strychnine Group.* In the treatment of circulatory disorders the use of nux vomica, containing strychnine and brucine, and of strychnine itself has been practically abandoned. While there is justification for this practice on the basis of the dosage used in the past, there is nevertheless a possibility that in higher therapeutic doses strychnine may be beneficial in restoring a normal vasomotor tone, particularly if the vasomotor collapse is caused by a depression of the vasomotor system. From a pharmacologic standpoint, certainly, strychnine is one of the best examples of a vasomotor stimulant. In animals with certain types of circulatory collapse one can restore the blood pressure at once by the intravenous administration of strychnine. In the intact mammal, not only evidence of cardiac slowing from vagus stimulation, but also a slight rise in the arterial pressure due to stimulation of the vasomotor center has been noted. In man, on the other hand, there is ample evidence that in the presence of a normally functioning cardiovascular system no appreciable changes are observed following subcutaneous administration of 0.5 to 2 mg. (gr. 1/100 to 1/30). No thorough study exists, however, so far as I know, indicating the effect of this drug in circulatory collapse following the administration of large therapeutic doses. In studying strychnine as a possible circulatory stimulant, it should be remembered that its beneficial effect cannot be judged solely from the changes in the heart rate and blood pressure. Until this problem is further investigated, however, we cannot afford to rely on strychnine in circulatory emergencies.

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